Remarks

Amendments to the Claims

The claims have been amended to be specific to dry powder formed of drug and diketopiperazines for nasal delivery. Dependent claims have been amended to be specific to the diketopiperazines recited at page 11, lines 9-10, and page 12, line 3. New dependent claims recite that the microparticles are made by spray drying. Support is found at page 6, line 21.

Rejection Under 35 U.S.C. § 102

Claims 1-4, 7-11 and 14-17 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,690,954 to Illum. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Illum

Illum describes a drug delivery system including a plurality of bioadhesive microspheres containing an active drug and an absorption-enhancing material associated with each microsphere for increasing the bioavailability of the drug (col. 5, lines 19-32; col. 4, lines 6-12). Representative uptake enhancers are phospholipids and lysophosphatidyl compounds (col. 4, lines 22-30). The microspheres are formed of a natural polymer such as a starch (col. 6, line 17) or any one of gelatin, casein, dextrans, alginate, ararose, albumin, collagen, chitosan, polyvinylacetate, and hyaluronic acid esters (col. 6, lines 17-20), which gel in contact with the mucosal surface (col. 6, lines 15-16). The microspheres have a size between 10 to 100 microns (col. 6, line 13).

Illum addresses the problem of decreased efficiency of nasal drug delivery due to rapid clearance of nasal sprays from the nose and inefficient drug absorption in the nasal cavity. Illum addresses these problems by designing a microsphere delivery system which has bioadhesive properties such that the microspheres will adhere to the nasal mucosa upon contact (col. 3, lines 2-9). Furthermore, the microspheres contain absorption enhancers which increase the bioavailability of the drug (col. 4, lines 6-12). The claimed subject matter improves retention of drug in the nasal mucosa by evaluating the aerodynamic properties of different sizes of microspheres and without the addition of any auxiliary components. The claimed subject matter furthermore addresses the systemic side effects of nasal administration such as somnolescence and bitter taste in the patient's mouth (p. 2, lines 2-16).

The claims are drawn to a composition for the nasal administration of a drug in a dry powder form consisting essentially of particles having an average particle size of between 10 and 20 microns, formed of drug and a diketopiperazine excipient in a dosage formulation suitable for administration to the nasal region and a method of using the composition. A critical aspect of the formulation is the range of its particle size between 10 and 20 microns (p. 2, lines 19-23), and the selection of a diketopiperazine. This **narrow range** of particle size is required to control the depth of penetration into the nasal system. The aerodynamic properties of the microspheres within this size range, such as weight-to-drag ratio, promote deposition of the microspheres in the nasal cavity. For example, a size below 10 microns could cause the composition to pass into the pulmonary region or mouth, which would result in a less efficient delivery of the drug and

cause undesirable side effects with certain type of drugs, e.g., bitterness in the case of an antihistamine. The claimed size range of between 10 microns and 20 microns allows a lower dosage to be administered, avoids or ameliorates the systemic side effects such as somnolescence due to lower dosage, and avoids the problem with bitter taste for drugs such as antihistamine (p. 2, lines 2-16). Furthermore, the claimed composition does not require addition of auxiliary absorption-enhancing materials.

Illum therefore does not anticipate the claimed invention for several reasons:

(a) Illum requires that the microspheres be formed from a biocompatible material that will gel in contact with the mucosal surface;

(b) Illum requires that the microspheres further contain an absorption enhancer;

(c) Illum does not disclose the claimed narrow aerodynamic range of particle size; and

(d) Illum does not disclose a diketopiperazine.

Furthermore, Illum teaches away from the claimed subject matter. Illum describes microsphere delivery systems wherein the microsphere size ranges between 10 and 100 microns. In order to avoid rapid clearance and ineffective drug absorption, the microspheres are formed from bioadhesive materials and equipped with an absorption enhancer. Illum therefore teaches away from administering drugs using 10-20 micron microspheres without absorption enhancers or bioadhesive materials. Illum teaches that the claimed subject matter would not remain in the nasal cavity. However, contrary to Illum's suggestion, the claimed subject matter is able to

effectively deliver drugs without typical side effects due to the aerodynamic properties of particles in the claimed size range.

Rejection Under 35 U.S.C. § 103

Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17 and 18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,503,852 to Steiner, et al. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Steiner

Steiner discloses several drug delivery systems using diketopiperazines and their analogs to form microparticles encapsulating a drug to be delivered. The microparticles may be microspheres with diameters ranging between 0.1 to 10 microns (col. 4, lines 32-40). The drug delivery system may be used to delivery biologically active agents having therapeutic, prophylactic or diagnostic activities, such as vitamins, minerals, amino acids and fats. In a preferred embodiment, the biologically active agents are to be released into the circulatory system after transport from the GI tract following oral delivery (col. 10, lines 25-32). Other delivery methods include enteral, parenteral, subcutaneous, intramuscular, intraperitoneal and topical delivery methods (col. 11, line 64 – col. 13, line 10). The microspheres may optionally be used in diagnostic applications, such as imaging the nasal and pharyngeal, gastrointestinal, and genitourinary tracts (col. 13, lines 12-24).

Steiner does not disclose drug delivery systems for nasal administration. Steiner does not disclose dispensing the composition using a nasal insufflator. While Steiner does mention that

the microparticles can include a diagnostic imaging agent useful for imaging the nasal tract, the microparticles are administered parenterally or enterally. Steiner does not mention or suggest a composition for nasal administration of a drug comprising microparticles having an average size of 10 to 20 microns. Steiner therefore does not address any problems associated with nasal administration of drugs, such as lack of retention of drug in the nasal mucosa, somnolescence, or bitter taste in the mouth. Steiner discloses microspheres with diameters ranging between 0.1 and 10 microns – this size range is not effective for improving the nasal administration of drugs. Microspheres below 10 microns will pass into the pulmonary region or mouth, resulting in a less efficient delivery of the drug and cause undesirable side effects with certain type of drugs, e.g., bitterness in the case of an antihistamine.

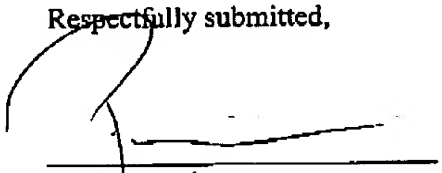
Steiner in fact teaches away from nasal delivery which requires adhesion to and uptake within the nasal region. Imaging is the exact opposite – where the object to be image is not taken up and not distributed systemically.

The claimed subject matter is therefore not obvious in view of Steiner. Steiner does not disclose nasal administration of drugs nor improvement of nasal administration. Steiner does not discuss the aerodynamic properties of the microspheres or other properties relevant to nasal administration. It is not obvious to modify the microspheres disclosed by Steiner such that they are suitable for nasal administration. Furthermore, Steiner does not propose studying aerodynamic properties of the microspheres so as to suggest ways to improve nasal

administration of drugs. Steiner clearly does not describe making microparticles of diketopiperazines by spray drying.

Allowance of claims 1-5, 7-12 and 14-18, as amended, and new claims 20 and 21, is respectfully solicited.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: April 12, 2004

HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (Fax)

1759973_v1